Pol J Aviat Med Psychol 2013; 19(4): 25-30

SHORT COMMUNICATION

HYPOTHALAMIC-PITUITARY SARCOIDOSIS - CLINICAL AND AVIATION-MEDICAL DECISION MAKING ASPECTS

Łukasz OLENDRZYŃSKI[1], Katarzyna PIĄTEK[2]

[1] Military Institute of Aviation Medicine, Clinical Center, Warsaw

[2] Poznan University of Medical Sciences, Department of Endocrinology, Metabolism and Internal Medicine, Poznan

Source of support: Own sources

Author's address: Łukasz Olendrzyński, MD, Military Institute of Aviation Medicine, ul. Krasinskiego 54/56, 01-755 Warsaw, Poland, e-mail: lolendrz@wiml.waw.pl

Background: Sarcoidosis is a multisystem disease of unknown etiology. It is characterized by the presence of noncaseating granulomas in the affected organs. Central nervous system involvement is observed in approximately 5% of patients. Granulomatous infiltration has a special predilection for the hypothalamus, pituitary gland, and, less commonly, pituitary stalk. Clinical symptoms include abnormal secretion of hormones of the anterior and posterior pituitary, including complete hypopituitarism. Neurosarcoidosis can mimic other, more common lesions. The mainstay of treatment is the use of steroids and supplements of the missing hormones. Despite the fact that hypothalamic-pituitary sarcoidosis is relatively rare, it should be taken into account in differential diagnosis during medical procedures in pilots and other aviation personnel. The variety of clinical symptoms that may occur in the course of neurosarcoidosis may lead to incorrect clinical diagnoses as well as significantly contribute to the reduction of flight safety.

Keywords: sarcoidosis, hypothalamus, pituitary, hormones, glucocorticoids

Table: 1 • **References:** 14 • **Full-text PDF:** http://www.pjamp.com • **Copyright** © 2013 Polish Aviation Medicine Society, ul. Krasińskiego 54/56, 01-755 Warsaw, license WIML • **Indexation:** Index Copernicus, Polish Ministry of Science and Higher Education

INTRODUCTION

Sarcoidosis, also known as Besnier-Schaumann-Boeck disease, is a generalized granulomatous disease of unknown etiology. Current knowledge is insufficient to either confirm or exclude genetic predilection in individuals with mutation in gene encoding for protein BTNL2, located within chromosome 6. The incidence rate is about 10/100,000/year, with highest morbidity being observed among African Americans, but also in Sweden and Iceland. Peak morbidity is observed between the age of 15 and 40; the disease is more common in women [2]. Granulomas may occur in lymph nodes, lungs, skin, liver, eyeballs, spleen, bones, muscles, heart as well as within the central nervous system (CNS). Lung lesions are detected in more than 90% patients [7].

Endocrinopathies occurring in the natural history of sarcoidosis are rare, being observed in 5% of patients. Most commonly, the disease affects the hypothalamus, the pituitary gland, and, less commonly, the pituitary stalk. In a vast majority of cases, neurosarcoidosis is concomitant to sarcoidosis of lungs, skin or liver [6].

Clinical symptoms of CNS involvement are observed in 5% of patients. However, autopsy examinations show that CNS lesions are present in as much as 25% of patients, suggesting a significant percentage of subclinical forms of the disease. Lesions in muscle biopsies or cerebrospinal fluid are detected in as much as 80% of asymptomatic patients with sarcoidosis [5]. Early detection of neurosarcoidosis is crucial as the disease is associated with high mortality rates. In 70% of patients with systemic sarcoidosis, CNS involvement is observed within 2 years from the onset of the disease.

Other possible endocrine manifestations of sarcoidosis should also be mentioned. Hypercalcemia is observed in about 5-10% of sarcoidosis patients. It is due to the increased production of 25-OH-vitamin D_3 within the granuloma [9]. Other endocrine disorders include hyperprolactinemia, chronic hypernatremia and hypovolemia in patients with diabetes insipidus symptoms who fail to replenish fluid deficits.

Regulation of the Ministry of National Defense dated 8 January 2010 contains a list of endocrine disorders restricting or voiding the qualifications of military aviation personnel to perform specific professional tasks (Tab. 1.).

Tab. 1. List of diseases and disabilities taken into account when assessing physical and emotional qualifications for professional military service in air, land air traffic control and aviation engineering.

Paragraph	Item	Disorder or disability	Health groups				
			pilots			flight crew	land personnel
			IA	IB	IC	II	III
53	1	Euthyreoid goiter of small size. Small thyroid nodules not impairing systemic health	N/C	C/N	C	C	C
	2	Euthyreoid goiter of significant size. Thyroid dysfunctions with or without goiter	N	N	N	N	N/C
	3	Status after thyroid surgery not impairing systemic health	C/N	C	C	C	C
	4	Status after thyroid surgery impairing systemic health	N	N	N	N	N
54	**1**	**Pituitary disorders**	**N**	**N**	**N**	**N/C**	**N/C**
	2	Adrenal gland disorders	N	N	N	N/C	N/C
	3	Parathyroid gland disorders	N	N	N	N/C	N/C
	4	Insulin-dependent diabetes	N	N	N	N	N
	5	Non-insulin-dependent diabetes requiring pharmacological treatment	N	N	N	N/C	N/C
	6	Glucose tolerance impairment	N/C	N/C	N/C	N/C	N/C
	7	**Other endocrine gland dysfunctions not impairing systemic health**	**C/N**	**C/N**	**C/N**	**C/N**	**C/N**
	8	**Other endocrine gland dysfunctions impairing systemic health**	**N**	**N**	**N**	**N**	**N**

CHAPTER XIII – ENDOCRINE GLANDS

In aviation medicine certification, diagnosis of pituitary sarcoidosis results in professional disqualification for medical reasons of all military pilots and significant professional restrictions in the remaining aviation personnel. It should be also highlighted that the cited regulation does not directly refer to endocrinopathies caused by hypothalamic injuries. In case of neurosarcoidosis, the hypothalamus is a central nervous system structure commonly involved by the pathological process. In addition, it is manifested by a diverse plethora of clinical symptoms. Some of these symptoms, such as somnolence, libido disorders, impotence, headaches, or thermoregulation disorders are usually not considered by patients as symptoms of a serious disease; in addition they may be not concealed in standard medical interviews for qualification-related reasons. Meanwhile, disorders of that type significantly affect overall systemic health, particularly in aviation personnel. Therefore, any clinical symptoms and endocrinopathies in the natural history of neurosarcoidosis should be assessed pursuant to Paragraph 54(8). It should also be mentioned that disturbances of vision due to the expansion of granuloma beyond the sella turica and accompanying impingement of the optic nerve may be the first symptoms diagnosed in CNS sarcoidosis. Thus, physicians of different specialties carrying out clinical qualification procedures in aviation medicine, i.e. endocrinologists, neurologists, ophthalmologists, laryngologists, psychiatrists and radiologists should consider sarcoidosis as the potential cause of abnormalities observed in their subjective examinations.

SYMPTOMS, DIAGNOSTICS AND DIFFERENTIATION

Symptoms of neurosarcoidosis depend on the size and location of granulomas. Within the CNS, sarcoidosis most commonly affects the hypothalamus, the pituitary, the third ventricle, cranial nerves and cerebral meninges (predilection to the involvement of hypothalamus as the main organ was observed in autopsy examinations). About 5-33% of neurosarcoidosis patients are diagnosed with diabetes insipidus and other symptoms of hypothalamic-pituitary function: somnolence, disturbed thermoregulation, increased body weight, impotence, decreased libido, hypogonadism, amenorrhoea, galactorrhea or hypopituitarism. Headaches, convulsions, and symptoms that mimic multiple sclerosis are common. Much less common symptoms include memory disorders, persistent hiccups, schizophrenic symptoms or acute strokes due to granulomas being present within blood vessels [1,3,6,11,12,13]. Hyperprolactinemia is observed in case of hypothalamus or pituitary stalk damage as a result of suppressed inhibition of dopamine secretion. Detection of hyperprolactinemia in the natural history of sarcoidosis may be considered a specific indicator of hypothalamic lesions.

The most common neurological symptom is the paralysis of one of the cranial nerves, particularly the facial nerve. Less commonly, ocular muscle paralysis and deafness due to the involvement of acoustic nerve are observed. Optic neuritis may also develop; however, it is a non-specific symptom. Pituitary sarcoidosis with optic nerve impingement may be manifested by bitemporal hemianopia. Ocular manifestations may also include iridocyclitis and choroiditis. Otherwise, the disease may be manifested by intra-axial or extra-axial tumors, involvement of cerebrospinal meninges and functional disorders of the hypothalamus and the pituitary [7,9].

Despite the significant progress in imaging techniques, histopathological examination remains the mainstay of sarcoidosis diagnostics. However, in some cases when the diagnosis of sarcoidosis, such as lung or lymph node sarcoidosis, is accompanied by the presence of neurological symptoms and brain MRI lesions typical for sarcoidosis, the diagnosis of neurosarcoidosis may be made without histopathological examination.

The MRI of the CNS and examination of the cerebrospinal fluid are important, and sometimes even decisive for diagnosing neurosarcoidosis. F18-FDG positron emission tomography (PET) is also a valuable tool for assessing lesions in the natural history of neurosarcoidosis.

Differential diagnosis of MRI-detected lesions and clinical symptoms should include malignant tumors (meningiomas, gliomas, metastases), other infiltrative/inflammatory diseases (histiocytosis X, most commonly involving hypothalamus and pituitary stalk) and granulomatous diseases (tuberculosis and syphilis). Primary tumors of the posterior pituitary are very rare. Occasional cases include granulomas, chordoma, gliomas and ganglioneuroma. More often, differentiation should include possible posterior pituitary metastases of pre-existing diffuse cancer.

Symptoms of diabetes insipidus should be differentiated from diabetes, nephrogenic diabetes insipidus, hypercalcemia and nephrocalcinosis [6].

Following abnormalities in investigational results are also observed in sarcoidosis: accelerated ESR, polyglobulia, hypercalcemia and hypercalciuria, elevated levels of $1.25(OH)_2D$, increased activity of ACE and elevated levels of S-IL-2R, elevated CD4/CD8 ratio.

AN OVERVIEW OF REPORTED CASES

The available literature contains very few studies of sarcoidosis of the hypothalamic-pituitary axis. Several dozens of cases of CNS sarcoidosis were described in recent 30-40 years. Most cases involved detection of brain MRI abnormalities in patients with previously diagnosed sarcoidosis of other organs. In many cases, brain MRI scans mimicked hypothalamic tumors, focal pituitary lesions or tumors expanding beyond the sella turica. Patients were examined for hormonal abnormalities, detecting numerous combinations of disorders.

Taking into account the anatomical structure of the hypothalamic-pituitary region, possible clinical symptoms and hormonal disturbances occurring when this brain region is affected by sarcoidosis are easily predictable. Most commonly reported abnormalities were associated with hypothalamic dysfunction manifested mainly as polydipsia and polyuria. The same symptoms are also observed upon damages to the posterior pituitary and the pituitary stalk. It is also worth mentioning that isolated damages of single structures within the anatomical region of interest were observed in rare cases.

Vesely, Stuart et al. described 29 cases of hypopituitarism in the natural course of sarcoidosis; diabetes insipidus was observed in 16 of these patients. Nine out of ten patients did not respond to stimulation tests, demonstrating pituitary damage. Partial response to stimulation with hypothalamic liberins was observed in one patient [6].

Langrand et al. performed a detailed assessment of 24 neurosarcoidosis patients from 7 clinical sites in France. The study group consisted of 10 females and 14 males. The average age at diagnosis was 31.5 years (8-69 years). Patients were included into the study on the basis of clinical symptoms, biopsies and head MRI scans. Sarcoidosis of the following organs was confirmed by histopathological examination of biopsies in 21 out of 24 patients: bronchi (12 cases), lymph nodes (6), pituitary gland (4), liver (3), testicle (2) as well as CNS, skin and kidneys (1 each). In 71% of cases, neurosarcoidosis was accompanied by sarcoidosis of the lungs [4].

Results of hormonal examination of patients were surprising, as dysfunction of at least one anterior pituitary hormone was detected in as many as 22 patients: reduced LH and/or FSH levels in 21 patients, reduced TSH levels in 15 patients, reduced GH levels in 9 patients, and reduced ACTH levels in 8 patients. Hyperprolactinemia was diagnosed in 12 patients. The same number of patients presented with manifestations of diabetes insipidus. Thus, the most common hormonal abnormality in the study group was reduced levels of gonadotropins and clinical symptoms associated with gonadotropin deficiencies, such as libido disorders, hypogonadism and secondary amenorrhea. The above finding is in contrast to previous data from neurosarcoidosis studies, where diabetes insipidus and hyperprolactinemia were the most commonly diagnosed symptoms [1,3,8,11,13]. During a 4-year follow-up of the study group, hormonal activity was restored following glucocorticoid treatment in as little as 2 patients. In 12 patients, improvements in the MRI image of the CNS were observed [4].

Prednisone at doses of 0.5-1.0mg/kg/day was used to treat 22 patients; later on, 9 patients required the dose to be increased (>1.5mg/kg methylprednisolone in intravenous infusions). In most patient the treatment led to an improvement in the MRI image; hyperprolactinemia resolved in some patients as well. However, no improvement in pituitary hormone secretion was observed in 22 out of 24 patients who still required supplementation of both the deficient anterior pituitary hormones and vasopressin [4].

It is worth mentioning that two cases of isolated hypothalamic-pituitary sarcoidosis were identified in the group of study patients.

In their study group of neurosarcoidosis patients, Porter et al. observed chest X-ray pathologies in as little as 30% while the remaining literature reports that cerebral and lung lesions are concomitant in about 70-90% [4,7,9]. In this group, autoimmunization features was observed in 19.2% of patients. Two cases of Addison's disease as an element of type II autoimmune polyglandular syndrome in (APS II) were identified, as were 13 cases of elevated anti-TPO antibody titers (two cases of Graves disease and six cases of Hashimoto disease were diagnosed in this subgroup) and 1 case of type 1 diabetes mellitus [9].

Loh et al. described a case of an isolated nodular mass within the posterior pituitary in a brain MRI scan with no abnormalities in other parts of the brain. Results of the anterior pituitary hormone determinations were normal, including the pro-

lactin levels. The only observed abnormality was vasopressin deficiency. Such hormonal test results suggested isolated involvement of the posterior pituitary, excluding hypothalamus and pituitary stalk. Otherwise, higher prolactin levels should be expected. The patient was preliminarily qualified for transsphenoidal biopsy of the pituitary tumor for the establishment of diagnosis. However, just before the procedure, suspicion of the sarcoidosis of lungs was made on the basis of abnormal chest X-ray, later confirmed by transbronchial biopsy of the lymph nodes. Taking into account the possibility of concomitant neurosarcoidosis, prednisone treatment was initiated at 40mg/day with intranasal desmopressin supplementation. One month after initiation of treatment, complete regression of MRI lesions was observed. Unfortunately, antidiuretic hormone (ADH) secretion disorders, i.e. diabetes insipidus, required continuation of desmopressin administration despite improvements in the radiological image [6].

TREATMENT

Glucocorticoids are efficacious in most cases. The mechanism of action of steroids in sarcoidosis consists in reduction of the CD4/CD8 ratio and interleukin 2 production with inhibition of collagen synthesis [10].

Cases of hypothalamic-pituitary sarcoidosis patients experiencing depression, reduced libido, hyponatremia and weight loss were reported. Besides these symptoms, hypopituitarism and hyperprolactimemia were observed. Prednisone 60mg/day and missing hormone replacement was used in these patients. After about 6 months of treatment, clinical improvement and resolution of radiological lesions was observed. Next, the steroid doses were reduced by 5mg every 2-3 until the final, maintenance level of 7.5mg/day was reached.

Neurological symptoms in the form of ataxia reoccurred in two patients following glucocorticoid dose reduction. The symptoms resolved after increasing the glucocorticoid dose was increased again. In long-term follow up, after 23 years all patients require supplementation with anterior pituitary hormones and the maintenance dose of 10mg prednisone/day.

The authors point out that in case neurosarcoidosis is diagnosed and accompanied by pituitary hormone secretion disorders, treatment with higher doses of glucocorticoids should last quite long and the dose reduction to reach the maintenance level should proceed slowly [10].

In some patients, recurrence of symptoms was observed as glucocorticoid dose was reduced to about 20-25mg/day. In cases of glucocorticoid resistance or when aiming at the reduction of the adverse effects of medications, attempts to use intravenous methylprednisolone pulses or inclusion of other drugs, such as cyclophosphamide, cyclosporine, azathioprine, chlorambucil, methotrexate, or hydrochloroquine are recommended [5]. If combination therapy fails, CNS radiation therapy should be considered. Targeted brain irradiation at low doses of 20 Gy may be used. In rare cases, whole brain irradiation (WBI) may be necessary [14]. In addition, neurosurgical intervention may be necessary in cases of hydrocephaly or increased intracranial pressure with the risk of intussusception.

SUMMARY

Following conclusions may be drawn from the analysis of the selected bibliography on sarcoidosis of the central nervous system. In a significant number of cases, treatment contributed to an improvement in the radiological CNS image, including complete lesion resolution. In most cases, glucocorticoid treatment led to resolution of hyperprolactinemia which is likely to be due to elimination of hypothalamus and pituitary stalk impingement by the lesion prior to the treatment. Glucocorticoid treatment may to some extent improve the secretion of hormones of the anterior pituitary. In most cases, however, proper hormone levels cannot be achieved. This is evidenced by the lack of endocrine response to stimulation with appropriate liberins both before and after glucocorticoid treatment.

In the context of aviation medicine, the diagnosis of neurosarcoidosis in aviation personnel most commonly leads to permanent damage to the affected brain structures despite the initiated treatment and requires constant hormonal supplementation. It also seems justified that future legislative works should include preparation of a more detailed list of endocrine gland disorders that might result in medical disqualification of aviation personnel.

AUTHORS' DECLARATION:

Study Design: Łukasz Olendrzyński, Katarzyna Piątek; **Data Collection:** Łukasz Olendrzyński, Katarzyna Piątek; **Manuscript Preparation:** Łukasz Olendrzyński, Katarzyna Piątek; **Funds Collection:** Łukasz Olendrzyński, Katarzyna Piątek. The Authors declare that there is no conflict of interest.

REFERENCES

1. Alam T, Thomas S. Diabetes insipidus secondary to sarcoidosis presenting with caseating granuloma. BMJ Case Rep 2011.
2. Herold G. Interna. Warszawa: PZWL; 2008.
3. Koji T. Sarcoidosis of the Hypothalamus and Pituitary. Internal Medicine 2004; 43:894-895.
4. Langrand C, Bihan H, Raverot G, Varron L, Androdias G, Borson-Chazot F, et al. Hypothalamo-pituitary sarcoidosis: a multicenter study of 24 patients. QJM 2012; 105:981-95.
5. Lawton FG, Shalet SM, Beardwell CG, Daws RA. Hypothalamic-pituitary disease as the sole manifestation of sarcoidosis. Postgrad Med J 1982; 58:771-2.
6. Loh KC, Green A, Dillon WP Jr, Fitzgerald PA, Weidner N, Tyrrell JB. Diabetes insipidus from sarcoidosis confined to the posterior pituitary. Eur J Endocrinol 1997; 137:514-9.
7. Miyoshi T, Otsuka F, Takeda M, Inagaki K, Otani H, Ogura T. An elderly patient with sarcoidosis manifesting panhypopituitarism with central diabetes insipidus. Endocr J 2007; 54:425-30.
8. Ogawa Y, Tominaga T, Ikeda H. Neurosarcoidosis manifesting as tremor of the extremities and severe hypopituitarism. Neurol Med Chir 2008; 48:314-317.
9. Porter N, Beynon HL, Randeva HS. Endocrine and reproductive manifestation of sarcoidosis. Q J Med 2003; 96:553–561.
10. Smith D, Cullen MJ. Two cases of hypothalamic- pituitary sarcoidosis. J R Soc Med 2005; 98:167–169.
11. Tabuena RP, Nagai S, Handa T, Shigematsu M, Hamada K, Ito I, Izumi T, Mishima M, Sharma OP. Diabetes Insipidus from Neurosarcoidosis. Intern Med 2004; 43:960-6.
12. Tanaka K, Yamamoto M, Okazaki K, Yamaguchi T, Sugimoto T. Partial Improvement of Anterior Pituitary Deficiency Following Steroid Treatment in a Patient with Neurosarcoidosis Accompanied by Central Diabetes Insipidus. Intern Med 2012; 51:2175-9.
13. Valeyre D, Chapelon-Abric C, Belin C, Dumas JL. Sarcoidose du système nerveux central. Rev Med Interne 1998; 19:409-14.
14. Zgliczyński W. Wielka Interna. Endokrynologia. Warszawa: Medical Tribune Polska; 2012.

Cite this article as: Olendrzynski L, Piatek K. Hypothalamic-Pituitary Sarcoidosis - Clinical and Aviation-Medical Decision Making Aspects. Pol J Aviat Med Psychol, 2013; 19(4):25-30.